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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/749,873	12/29/2000	Toshihiko Ohtomo	053466/0294	6722

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EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	11

DATE MAILED: 11/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application N .	Applicant(s)	
	09/749,873	OHTOMO ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 40-57* is/are pending in the application.

4a) Of the above claim(s) *1,44-47 and 53-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-43 and 48-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *08/646,265* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2.5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 40-43, 48-52 in Paper No. 9 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1, 44-47, 53-57 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Election was made and treated without traverse in Paper No. 9.

3. Claims 40-43, and 48-52 are under examination.

Specification

4. The disclosure is objected to because of the following informalities:

a. The first line of the specification should indicate that application 08/646,265 is now U.S. Patent 6,214,973.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 40-43, 48-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 40-43, 48-52 are indefinite for reciting a method of making a reshaped antibody in claim 40 and a method of making a single-chain Fv in claim 48 because the claims do not recite method steps. It is unclear what steps are required to make the functional antigen binding site in claims 40 and 48.

b. claims 40-43 and 48-52 are indefinite for reciting "derived" in claims 40 and 48. The term "derived" is not one which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. The primary deficiency in the use of this phrase is the absence of an ascertainable meaning for said phrase. Since it is unclear how the CDRs or the framework regions are to be derivatized to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said phrase. Further, it is not clear whether the "derived" CDRs or frameworks are formed by attachment of a detectable marker, therapeutic molecule, some other molecule or altering the amino acid sequence, for examples. In addition, since the term "derived" does not appear to be clearly defined in the specification, and the term can encompass proteins with amino acid substitutions, insertions, or deletions, antibody fragments, chemically derivatized molecules, or even antibody mimetics. In absence of a single defined art recognized meaning for the phrase and lacking a definition of the term in the

specification, one of skill in the art could not determine the metes and bounds of the claims.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

8. Claims 40-42, 48-50 are rejected under 35 U.S.C. 102(b) as being anticipated by Adair et al (WO 91/09967, published 7/91, IDS #2 ½).

The claims recite a method for making a reshaped human antibody or a single chain FV comprising CDRs from a mouse and framework regions from a human antibody wherein residue 46 of the L chain is a mouse residue and residue 94 of the H chain is a mouse and residues 27-30 are additional mouse residues, wherein the single-chain comprises a H chain V region and a L chain V region which is linked by a linker.

Adair et al teach a method to produce humanized and single-chain antigen binding fragment comprising mouse CDRs and human frameworks wherein residues 46

of the light chain is a mouse residue and residues 27-30 and 94 of the heavy chain is mouse residues (see page 10, page 17-18, 20, 22). Adair et al also teach residues 26-35 of the H chain are in the CDRs and as such it is inherent that these residues (which include 27-30) would be mouse residues.

9. Claims 40, 43, 48, and 51 are rejected under 35 U.S.C. 102(e) as being anticipated by Seemann et al (U.S. Patent 5,645,817, Con to 8/93).

Claims 40 and 48 have been described supra. Claim 43 and 51 recite wherein residue 46 is proline.

Seemann et al teach a method of producing a humanized and humanized single-chain antigen binding fragment which comprises transfer of the CDRs of the mouse antibody to human frameworks wherein residue 46 in the light chain is a proline (see column 2, lines 35-39, column 3, lines 10-15, column 11, lines 15-20).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 40-43, 48-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adair et al (WO 91/09967, published 7/91, IDS 2 ½) as applied to claims 40-42, 48-50 above, and further in view of Seemann et al (U.S. Patent 5,645,817, CON to 8/93) and Huston et al (WO 88/09344, published 12/88).

Claims 40-43, 48-51 have been described supra. Claim 52 recites wherein the linker is SEQ ID NO:111.

Adair et al has been described supra. Adair et al does not teach residue 46 in the light chain is proline or a linker of SEQ ID NO:111. These deficiencies are made up for in the teachings of Seeman et al and Huston et al.

Seemann et al has been described supra.

Huston et al teach methods of humanization and producing single-chain Fv proteins which comprise a VL and a VH region and a linker of (gly-gly-gly-gly-ser)3 which is SEQ ID NO:111 in the instant application (see page 7).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method of producing a reshaped antibody or reshaped single-chain Fv wherein residue 46 in the L chain is a proline and residues 94, 27-30 are mouse residues and the linker in the single-chain FV is SEQ ID NO:111.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method of producing a reshaped antibody or reshaped single-chain Fv wherein residue 46 in the L chain is a proline and residues 94, 27-30 are mouse residues and the linker in the single-chain FV is SEQ ID NO:111 because Adair et la teach a method of humanization with residues 46 in the light chain being a donor residue and Seemann et al teach residues 46 in the light chain must be a proline which is the mouse donor residue and both of Adair and Seemann teach single-chain antigen binding fragments with linkers. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method of producing a reshaped antibody or reshaped

single-chain Fv wherein residue 46 in the L chain is a proline and residues 94, 27-30 are mouse residues and the linker in the single-chain FV is SEQ ID NO:111 because Huston et al teach single-chain antigen binding fragments and the linker is (gly-gly-gly-gly-ser)3 which exhibited good binding compared to linkers of (gly4-ser)1 and (gly-4-ser)5 (see page 52).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

12. Claims 40-43, 48-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moriuchi et al (British J. Cancer 68:831-837, 11/12/93, Ids # 2 ½) as evidenced from the specification and further in view of Adair et al (WO 91/09967, published 7/91, IDS 2 ½) and Huston et al (WO 88/09344, published 12/88).

The claims have been described supra.

Moriuchi et al teach a mouse antibody ONS-M21 and the antibody is directed against a cell surface antigen and the antibody has application in human diagnostics and therapeutics. Moriuchi et al does not teach humanization of the antibody or single-chain antibodies or a linker of SEQ ID NO:111. These deficiencies are made up for in the teachings of Adair et al and Huston et al.

Adair et al has been described supra.

Huston et al had been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method of producing a

reshaped antibody or reshaped single-chain Fv wherein residue 46 in the L chain is a proline and residues 94, 27-30 are mouse residues and the linker in the single-chain FV is SEQ ID NO:111.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method of producing a reshaped antibody or reshaped single-chain Fv wherein residue 46 in the L chain is a proline and residues 94, 27-30 are mouse residues and the linker in the single-chain FV is SEQ ID NO:111 because Adair et al teach a method of humanization with residues 46 in the light chain being a donor residue and Moriuchi et al teach the ONS-M21 antibody which as evidenced from the specification the ONS-M21 antibody of Moriuchi et al is the same antibody as that described in the specification (see page 5-6) and as such it would be obvious that the murine residue at position 46 is a proline. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method of producing a reshaped antibody or reshaped single-chain Fv wherein residue 46 in the L chain is a proline and residues 94, 27-30 are mouse residues and the linker in the single-chain FV is SEQ ID NO:111 because Huston et al teach single-chain antigen binding fragments and the linker is (gly-gly-gly-gly-ser)3 which exhibited good binding compared to linkers of (gly4-ser)1 and (gly-4-ser)5 (see page 52).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

15. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879